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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,277	03/30/2001	Wen-Tien Chen	178-295 CIP	7294

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HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	4

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,277	CHEN, WEN-TIEN	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *1-9,12-26 and 28-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11,27 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-63* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The election filed August 1, 2002 in Paper No. 10 is acknowledged and has been entered. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The amendment filed August 1, 2002 in Paper No. 10 is acknowledged and has been entered. Claim 63 has been added.

3. Claims 1-63 are pending in the application. Claims 1-9, 12-26, and 28-62 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 10, 11, 27, and 63 are currently under prosecution.

Compliance to Sequence Rules under 37 CFR §§ 1.821-1.825

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

Examples of disclosed sequences that are of sufficient length to fall under the requirements set forth in 37 CFR §§ 1.821-1.825 appear on page 21 in line 7 and on page 30 in lines 3 and 4.

Applicant is given the period of time within which to reply to this Office action to place this application in compliance with the requirements set forth under 37 CFR §§

1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g).

Applicant is requested to return a copy of the attached Notice to Comply with the response.

Specification

6. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include TAXOL (page 12), MATRIGEL (page 20), ADRIAMYCIN (page 24), AMICON (page 25), DERMALON (page 26), BAND-AID (page 26), KRAZY GLUE (page 33), AMERICLEAR (page 34), and COSMO BIOSCIENCE (page 34).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 10, 27, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Duke-Cohan, et al (*Blood* **82**: 2224-2234, 1993).

Duke-Cohan, et al teach a bispecific antibody that comprises an binding domain that binds to CD26, i.e., dipeptidyl peptidase IV. Duke-Cohan, et al teach a composition comprising the purified antibody and PBS.

Claims 27 and 63 are drawn to the bispecific antibody of claim 10, which is formulated as a pharmaceutical composition. However, the recitation requiring the bispecific antibody to be formulated as a pharmaceutical composition is viewed as a recitation of intended use. Since a recitation of intended use is not given weight in comparing the product of the prior art and the product of a claim, claims 27 and 63 read on the ingredient of the pharmaceutical composition, *per se*, which is a bispecific antibody according to claim 10.

Thus, all the limitations of the claims are thus met by the teachings of the prior art.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 10, 11, 27, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,545,405-A in view of US Patent Nos. 6,193,968-B1 and 5,753,230-A, Cheng, et al (*Journal of Biological Chemistry* **273**: 24207-24215, 1998), Johnson, et al (*Journal of Cell Biology* **121**: 1423-1432, 1993), Arao, et al (*Pancreas* **20**: 129-137, 2000), Masumoto, et al (*Hepatology* **29**: 68-74, 1999), Klominek, et al (*International Journal of Cancer* **72**: 1034-1044, 1997), Lundstrom, et al (*Biochemical and Biophysical Research Communications* **250**: 735-740, 1998), Fukushima, et al (*International Journal of Cancer* **76**: 63-72, 1998), Abdel-Ghany, et al

(*Invasion & Metastasis* **18**: 35-43, 1998), and Elble, et al (*Current Topics in Microbiology and Immunology* **213**: 107-122, 1996).

US Patent No. 5,545,405-A ('405) teaches: "In a method for treating a human suffering from cancer by administering a therapeutically effective amount of a whole glycosylated recombinant human, chimeric, CDR grafted or bispecific antibody effective in treating said cancer, wherein the improvement comprises an antibody glycosylated by a Chinese hamster ovary cell" (claim 1). '405 teaches pharmaceutical compositions for treating cancer comprising a bispecific antibody and a pharmaceutically acceptable carrier.

However, '405 does not teach a bispecific antibody that binds specifically to an epitope of dipeptidyl peptidase IV or CD26, and to an epitope of seprase, MT1-MMP, MMP-2 or $\alpha_3\beta_1$-integrin. Additionally, '405 does not teach that such a bispecific antibody can be formulated as a pharmaceutical composition, which can be used to inhibit angiogenesis or cancer invasion.

US Patent No. 6,193,968-B1 ('968) teaches a method for inhibiting tumor metastasis comprising administering to a subject an antibody that binds specifically to $\alpha_v\beta_1$-integrin (claim 6, for example). '968 teaches the antibody can be a bispecific antibody. In addition, '968 teaches that metastasis occurs by tumor cell invasion, which is a three step process comprising tumor cell attachment to extracellular matrix, proteolytic dissolution of the matrix, and movement of the cells through the dissolved barrier. '968 discloses that the prior art taught that antagonists of integrins provide a means for treating cancer by interfering with tumor cell adhesion to impede tumor metastasis. Furthermore, '968 teach that antagonists of integrins provide a means for inhibiting angiogenesis.

US Patent No. 5,753,230-A teach a method for inhibiting angiogenesis of a solid tumor in a patient comprising administering to the patient an antibody that binds specifically to $\alpha_v\beta_1$-integrin (claim 1, for example).

US Patent No. 6,123,941-A teach a method for reversing the malignant phenotype in tissue by administering to a subject an antibody that binds a β1 integrin (claim 1). '941 teaches the antibody can bind to $\alpha_3\beta_1$-integrin.

Cheng, et al teach that dipeptidyl peptidase (DPP) IV is an adhesion receptor for fibronectin, which is expressed at the surface of breast cancer cells. Cheng, et al teach that DPP IV mediates lung colonization by breast cancer cells. Cheng, et al disclose that the interaction of DPP IV with fibronectin may be a common mechanism by which lung metastasis initiates. Cheng, et al teach that an antibody that interferes with the interaction of DPP IV and fibronectin inhibits the adhesion of tumor cells to block tumor cell metastasis of the lungs.

Johnson, et al teach a monoclonal antibody that binds dipeptidyl peptidase IV, which is capable of inhibiting the specific adhesion of lung-derived vesicles to breast and prostate metastases of the lung.

Arao, et al teach the β1 integrins, including $\alpha_3\beta_1$-integrin play an essential role in adhesion and invasion of pancreatic cancer cells. Arao, et al teach that an antibody that binds β1 integrins blocks invasion of these cells.

Masumoto, et al teach the role of β1 integrins, including $\alpha_3\beta_1$-integrin in adhesion and invasion of hepatocellular cancer cells. Masumoto, et al teach that an antibody that binds β1 integrins blocks invasion of these cells.

Klominek, et al teach the role of β1 integrins, including $\alpha_3\beta_1$-integrin in adhesion and invasion of mesothelioma cells. Klominek, et al teach an antibody that binds β1 integrins to block cell adhesion, chemotaxis, and haptotaxis of these cells, whereas an antibody that binds the α3 subunit blocks chemotasis.

Lundstrom, et al teach the role of $\alpha_3\beta_1$-integrin in adhesion of breast cancer cells to cortical bone matrix. Lundstrom, et al teach that an antibody that binds the α3 subunit blocks attachment of these cells.

Fukushima, et al teach the role of $\alpha_3\beta_1$-integrin in adhesion, migration, and invasion of malignant glioma cells. Fukushima, et al teach that an antibodies that binds the α3 or β1 subunits block adhesion and migration of these cells.

Abdel-Ghany, et al teach the role of dipeptidy peptidase IV (DPP IV) in adhesion and metastasis of breast cancer cells. Abdel-Ghany, et al teach that the interference of DDP IV-mediated cell adhesion inhibits metastasis.

Elble, et al review the role of dipeptidy peptidase IV (DPP IV) in lung metastasis.

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art to have derived the claimed invention, because it would have been obvious to use a bispecific antibody that binds dipeptidyl peptidase IV and $\alpha_3\beta_1$-integrin in practicing the method of US Patent No. 5,545,405-A since US Patent Nos. 6,193,968-B1, 5,753,230-A, and 6,123,941-A teach that an antibody that binds to a β1 integrin, including an antibody that binds $\alpha_3\beta_1$-integrin, can be used to inhibit cancer cell invasion and angiogenesis, while the teachings of Arao, et al, Masumoto, et al, Klominek, et al, Lundstrom, et al, and Fukushima, et al provide evidence that such antibodies can effectively block the adhesion, migration, and invasion of a variety of malignant cells, and Cheng, et al, Johnson, et al, Abdel-Ghany, et al, and Elble, et al teach the role of dipeptidyl peptidase IV in metastasis and demonstrate that an antibody that binds dipeptidyl peptidase IV can inhibit metastasis by blocking adhesion, migration, and invasion. One of ordinary skill in the art at the time the invention was made would have been motivated to derive a bispecific antibody that binds $\alpha_3\beta_1$-integrin and dipeptidyl peptidase IV to treat cancer by inhibiting invasion and/or angiogenesis.

Conclusion

11. No claims are allowed.

12. The art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent No. 6,258,597-B1 teaches an inhibitor of dipeptidyl peptidase IV (DPIV), which can be a bispecific antibody that binds specifically to DPIV. Kotani, et al teach the diagnostic usefulness of a monoclonal antibody that binds dipeptidy peptidase IV. Schroder, et al teach the diagnostic usefulness of a monoclonal antibody that binds CEA. Barbet, et al teach the diagnostic usefulness of a bispecific antibody that binds

CEA and DTPA. Ghersi, et al teach a critical role of dipeptidyl peptidase IV in endothelial cell migration in response to wounding.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

S. Rawlings
STEPHEN RAWLINGS

slr
May 29, 2003